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| 10/808,880 | 03/24/2004 | Steven M. Watkins | 475512000400 | 7468 |

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| EXAMINER | |
|---|---|
| SAUCIER, SANDRA E | |
| ART UNIT | PAPER NUMBER |
| 1651 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/808,880 | WATKINS, STEVEN M. | |
| | Examiner | Art Unit | |
| | Sandra Saucier | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,8,10-14,21,22,26-41 and 61-63* is/are pending in the application.

4a) Of the above claim(s) *10,29,30,36 and 38-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,11-14,21,22,26-28,31-35,37 and 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 8, 10-14, 21, 22, 26-41, 61-63 are pending. Claims 1, 8, 11-14, 21, 22, 26-28, 31-35, 37, 61-63 are considered on the merits. Claims 10, 29, 30, 36, 38-41 are withdrawn from consideration as being drawn to a non-elected invention.

***Election/Restriction***

The elected species are directed to a method to determine if a pharmaceutical, nutritional, genetic, toxicological or environmental treatment, regimen or dosage influences *de novo* fatty acid synthesis in liver tissue as determined from the quantitation of palmitoleic or palmitic acid in the cholesterol ester fraction in plasma.

Please note that the election of species does not include the determination of *de novo* FA synthesis in adipose tissue.

Also, the examiner erred in indicating that claim 30 was under examination in the previous office action. It is dependent on a withdrawn claim and is, therefore, also not examined.

***Claim Rejections - 35 USC § 112***

ENABLEMENT

Claims 1, 8, 11-14, 21, 22, 26-28, 31-35, 37, 61-63 remain/are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for assessing *de novo* fatty acid synthesis in a liver tissue (elected species) by quantifying a marker in the cholesterol ester fraction of blood. Further, the specification does not provide for a correlation with any disease state or propensity for weight gain or compatibility, etc..

Platelets, red cells, leukocytes are all blood products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

For example, one would not reasonably assume that *de novo* fatty acid synthesis in the liver could be assessed by sampling the fatty acid content of platelets nor does the specification teach such relationships. However, this is the breadth of the independent claim.

Further, the specification does not teach a correlation between, for example menopause or auto immune diseases or aging, for example, see page 62 where a list of diseases or conditions are listed. However, no positive correlation of any condition or disease with any fatty acid "marker" appears to be demonstrated. Thus, the independent claim which is open to further steps or determinations encompasses associating menopause or ageing, for example with fatty acids.

The exemplification is of mice from which plasma, adipose, liver and heart samples have been substantially completely analyzed for lipid class and types. It appears in Experiment 1 that mice have been administered rosiglitazone and extracts from the tissues analyzed in each lipid class for fatty acid identity and concentration. However, no persistent correlation with at least one of applicant's elected species, 16:0, 16:1n7 appears in the cholesterol ester class (elected species) from plasma and established *de novo* synthesis in the liver.

The specification, while perhaps describing a methodology of complete lipid type and identity analysis and philosophical hypothetical predictions of usefulness or potential, fails to correlate any of the claimed, broad classifications with a consistent variation in cholesterol ester palmitate or palmitoleate from plasma with *de novo* fatty acid sythesis changes in the liver.

In fact, example 1 demonstrates that administration of the drug, rosiglitazone, decreases the content of palmitate in the ester fraction of cholesterol esters isolated from plasma from 140.4 ± 19.7 to 113.0±4.0, while the content of palmitoleic acid increases from 114.1±12.4 to 200.8± 39.4. In the liver, which is supposed to be the target tissue for *de novo* synthesis which

is supposed to be predicted by the plasma values, the mass of total fatty acids in the liver in all classes added together appears to increase by a significant amount. The specification fails to teach what the correlation is, for example is it a positive one or a negative one or a neutral one when menopause takes place as opposed to pre or post menopausal periods or when one has a "propensity" to gain weight or when an environmental treatment is not "compatible" what ever that means to a subject.

With regard to feeding the drug, CL 316,243 to mice in example 2, the plasma cholesterol palmitate content in the control is 144.8±7.0 and decreases to 114.4± 10.3 in the treated mice, while the 16:1n7 content of plasma cholesterol palmitate is 228.6±23.2 and decreases to 84.9± 31.5 in the treated group. The *de novo* fatty acid synthesis in the liver, at least from an analysis of total fatty acid content, appears to be uneffected. Since experimental mice have tightly controlled diets and should have been paired fed for the experiment since the effect of diet on lipid content of the animal is well known, variation of total fatty acid content from the control to experimental should be some sort of measure of *de novo* synthesis.

In short, the specification fails to show that there is a consistent correlation between *de novo* total fatty acid synthesis in the liver and the palmitic acid or palmitoleic acid content of the cholesterol ester fraction in plasma (mass or accumulation or concentration) and further fails to show what correlation exists for any disease, condition, genetic, toxicological or environmental treatment, etc..

The state of the art with regard to a correlation between a weight gain or loss due to a nutritional treatment and a change in a marker of *de novo* fatty acid synthesis in a tissue as in one embodiment of the claimed invention is undeveloped.

With regard to the claims where a method of determining whether a treatment will cause weight gain or loss; weight gain is not only dependent on

*de novo* fatty acid synthesis, but also on fatty acid oxidation. See Kusunoki *et al.* [U], "Modulation of Fatty Acid Metabolism as a ***Potential*** Approach to the Treatment of Obesity and the Metabolic Syndrome" (italics are mine).

Nutrition Reviews 1991 [V] states that there is no difference in *de novo* fatty acid synthesis due to non-insulin dependent diabetes, (page 255). Thus, in claim 42, for example, neither the specification nor the state of the art provides a correlation with propensity, risk or metabolic basis for diabetes.

*De novo* fatty acid synthesis is depressed in animals consuming a high fat diet; however, these animals may gain weight even though *de novo* fatty acid synthesis is depressed. An animal on a low-fat, high carbohydrate diet may have elevated *de novo* synthesis and weight gain, see the review by Parks *et al.* [W]. Thus, *de novo* fatty acid synthesis has not been shown to be correlated with the propensity, risk or metabolic basis for weight gain or loss either by the specification or the state of the art.

Guo *et al.* [X] teach that *de novo* lipogenesis under eucaloric or hypocaloric conditions occurs mainly in the liver, while under hpercaloric conditions adipose tissue is the site of appreciable *de novo* synthesis (discussion).

Thus, no correlation has been taught by either the specification or the prior art between *de novo* fatty acid synthesis as measured by the mass or quantity or concentration of palmitic or palmitoleic acid in plasma to demonstrate *de novo* fatty acid synthesis in the liver with disease or condition or any propensity for success in a treatment.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

As set forth in In re Fisher, 427 F2.d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. Ex parte Humphreys, 24 USPQ2d, 1260.

***Response to Arguments***

Applicants argue that the results in Table 5 show a correlation between rosiglitazone treatment, which is known to increase *de novo* fatty acid synthesis and palmitoleic and palmitic acid content of cholesterol esters in plasma. However, applicants have not provided evidence AT TIME OF FILING that it was known that rosiglitazone administration increases *de novo* fatty acid synthesis. It is noted that applicants' earliest priority date is 9/24/01.

The specification states that the concentration of palmitoleic acid in the cholesterol ester fraction of plasma increases with administration of rosiglitazone, which drug, incidently, has multiple effects on an intact animal including weight gain and effects on plasma glucose concentrations.

Applicants have not positively linked weight gain to increased *de novo* FA synthesis in liver. Weight gain may be a consequence of the type of diet, even though *de novo* synthesis of fatty acids is not increased in the liver, see Parks et al. and Guo et al. above.

Correlating or assessing appear to be mental steps. It is noted that the claim has only one active step, quantifying. Please see *Lab. Corp v. Metabolite Lab.* 79 USPQ2d 1065 (Supreme Court June 22, 2006) and *Classen Immunotherpies v. Biogen*, (pending CAFC case 06-1634), where the fact patterns are similar in that "correlating, noticing, assessing" are mental steps

which are performed after a well known active step such as measuring, determining, quantifying, etc. is performed. While no final legal determination has yet been made as to whether or not such methods are eligible subject matter under §101, these cases are brought to applicants' attention in order to promote a more positive and robust claim.

In *Metabolite Laboratories Inc. v. Laboratory Corp. of America Holdings*, 71 USPQ2d 1081 (Fed. Cir. 2004), the CAFC concluded that claims to methods of assaying or diagnosing require a "correlating" step in which a particular test result is correlated **unambiguously** with a particular conclusion. See *Metabolite Labs* at 1088. There is no unabiguous "correlation" with weight gain or with any disease process or even with merely *de novo* fatty acid synthesis that has been demonstrated. Merely that when prediabetic mice are administered rosglitazone, they have elevated palmitoleic acid content in the cholesterol ester fraction of plasma. This is not what is being claimed.

Further, the claim states that it is a method of assessing.... by quantifying.... The claim fails to state how the "quantifying" leads to or is correlated with the "assessing" which is required by the preamble.

The specification fails to teach what the specific correlation to the specific disease state or risk or propensity is and instead relies on the reader to form opinions as what the correlation or assessment might be. This is not enablement, but rather an attempt to claim a method in which any outcome would fall under its scope.

Applicant presents some additional studies in a declaration in an attempt to show an unambiguous correlation of both CE16:In7 and the ratio of CE 16:1n7/CE16:0 in the blood to the increase/decease of fatty acid synthesis in the liver.

The declaration has been carefully considered with the following results.

Study A shows that db/db mice administered rosiglitazone have elevelated plasma CE16:1n7. It appears that the leptin knockout, a genotype known to gain weight (db/db mice), do not have elevated plasma CE16:1n7 when not administered rosiglitazone even though these mice appear to show elevated FAS expression. Thus, while demonstrating that elevated CE16:ln7 and the ratio of CE16:1n7/CE16:0 is correlated with rosiglitazone administration to db/db mice, this experiment fails to demonstrate a correlation with any disease state or with weight gain or with FAS expression. Further, in the arguments on page 12, it is stated that rosiglitazone is a known inducer of *de novo* fatty acid synthesis in the liver and adipose tissue. However, this increase in FAS expression does not appear to be correlated with plasma CE16:1n7 in db/db mice or with plasma CE 16:1n7 in db/+ mice administered rosiglitazone in Exhibit 2. Also, all references sumitted by applicant which support the statement that rosiglitazone is a "known" inducer of fatty acid synthesis are post filing dates, which do not support the statement that it was known AT TIME OF FILING.

In exhibit 3, an undisclosed drug, said to be a PPAR gamma agonist (which is not rosiglitazone) was given to ZDF (Zucker diabetic fatty) rats in an undisclosed quantity for an undisclosed length of time. Weight gain and plasma CE16:1n7, CE 16:0 was measured in the rats over this undisclosed period of time. The Zucker diabetic fatty rats administered the undisclosed PPAR gamma agonist has elevated plasma CE16:1n7 and CE16:ln7/CE16:0 ratios and gained weight. However, all of the Zucker diabetic fatty rats gained weight, while only those administered PPAR gamma or PPAR delta agonist of undisclosed identity showed elevated CE16:1n7 levels. This experiment demonstrates at best, that Zucker diabetic rats all gained weight over the course of the experiment. Those administered PPAR gamma agonist of undisclosed identity gain more weight and have a higher plasma CE16:1n7 level. However, this does not establish a correlation that is unabiguous with weight gain, since all animals gained weight; however, not all animals exhibited elevated plasma CE16:1n7 levels. Thus, no consistent, clear correlation is shown between weight gain and plasma CE16:ln7 levels. These animals are

also of a genetic type which develop obesity and diabetes, and thus all have a propensity for weight gain and diabetes, which does not appear to be correlated with elevated marker levels. Also, no measurement of FAS activity, which may be agued to be an unambiguous indicator of increased *de novo* synthesis in liver, is shown.

Study C is another study where rosiglitazone is administered to humans, which shows that rosiglitizone increases CE16:1n7 levels in plasma. No correlation is seen between weight increases in the control (not administered rosiglitizone) and CE16:1n7 plasma levels is shown.

Study D shows that under caloric restriction, of undisclosed degree, CE16:1n7 levels in plasma are decreased. It is difficult to understand how this study is related to the claimed methods because the example is not related to the propensity, risk or metabolic basis for obesity. Nor is the example related to lipogenesis since at page 31 of the specification, it is stated that fasting increases de-novo lipogenesis in the liver. However, according to Study D, CE16:1n7 levels are decreased.

If applicant would concentrate on clearly demonstrating and claiming a positive, consistent and unambiguous numerical relationship between fatty acid synthtase activity in the liver, which may be argued to be a positive indicator of increased *de novo* fatty acid synthesis in liver to the levels of palmitoleic acid in the cholesterol ester fraction of plasma, prosecution might be advanced.

No claims are allowed.

## *Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is

filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed. Applicants should also keep in mind the elected species when amending claims and in arguments.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to the office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday, Tuesday, Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sandra Saucier
Primary Examiner
Art Unit 1651
September 11, 2007